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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,129	06/01/2006	Masato Nakano	TC00006USW	2654

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EXAMINER

ANDERSON, REBECCA L

ART UNIT	PAPER NUMBER
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1626

NOTIFICATION DATE	DELIVERY MODE
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04/03/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/596,129	Applicant(s) NAKANO ET AL.	
	Examiner REBECCA L. ANDERSON	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 7 is/are rejected.
- 7) ☒ Claim(s) 6 and 7 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>6/1/06</u> . | 6) <input checked="" type="checkbox"/> Other: <u>PTO-notice to comply with sequence disclosure requirements.</u> |

DETAILED ACTION

Claims 1-7 are currently pending in the instant application. Claims 1-5 and 7 are rejected and claims 6 and 7 are objected.

Claim Objections

Claim 6 is objected to because of the following informalities: Specifically, claim 6 has the term “and” twice in the claims. It is suggested that one instance be removed and replaced with a semi-colon. Appropriate correction is required.

Claim 7 is objected to because of the following informalities: Specifically, the second instance of the term “compound” is spelled incorrectly as “comopund”. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As stated in the MPEP 2164.01 (a), “There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.”

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,

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4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

1-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of the formula I and salts thereof does not reasonably provide enablement for a solvate thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

In the instant case, the claims are read as the compound, salts, or solvate.

The state of the prior art and the predictability or lack thereof in the art

In regards to the solvate form of the compound according to Byrn, et al., “the occurrence of hydrated or solvated crystal forms, crystals in which solvent molecules occupy regular positions in the crystal structure, is widespread but *by no means universal among drug substances.*” (emphasis added). Byrn, et al. “Solid State Chemistry of Drugs”, 2d ed., SSCI, Inc., Ch. 10 Polymorphs, pp. 232-247, 232 (1999). Most drug crystals that fall into the category of solvates are hydrates. *Id.* at 236.

While the level of skill in pharmacology and organic chemistry is exceedingly high, there is no absolute predictability as to which solvates will function as intended. Byrn notes that the water molecule is particularly suited to fill structural voids, due to its small size. *Id.* In hydrated crystal structures, water molecules bind to other water molecules but also to any available functional group, i.e. carbonyls, amines, alcohols,

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and many others which are capable of accepting or donating an active hydrogen atom to form hydrogen bonds. *Id.* Also, the behavior of hydrates of pharmaceuticals is unpredictable due to dehydration prior to melting, and cracking during dehydration. *Id.* at 234. Too, hydrates and solvates may only be formed under certain conditions, dependent upon the compounds sought to be crystallized. Such a process is not a given in pharmacology and requires a great deal of research, with no guarantee of success.

Furthermore, the stability of solvates and hydrates is not altogether predictable, wherein said stability directly affects the properties of a given molecule. This lack of stability means a hydrate or solvate, if found to possess similar properties as the target compound, may not function as intended *in vivo*. Such facts lead to the conclusion that more than a mere recitation is needed in order to support a claim to solvates and hydrates. Creating functional solvates and hydrates with the same properties as the mother-compound is by no means routine, thus there must be a showing sufficient to satisfy the enablement requirement.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present is for the compounds and salts thereof.

The breadth of the claims

The breadth of the claims includes the compound, salts and solvated.

The quantity of experimentation needed and the level of the skill in the art

The level of difficulty required to produce functional hydrates and solvates is extremely high. The level of skill in pharmacology/organic chemistry is also very high. However, despite such a high level of skill in the requisite art, the creation of solvates and hydrates is unpredictable to the extent that undue experimentation is required in order to make and use solvates and hydrates of the claimed compounds. There is an insufficient showing in the Specification, or the state of the art does not acknowledge that the solvates and hydrates of the claimed compounds can be created via routine experimentation.

Therefore, Applicant's Specification does not enable one of ordinary skill in the art to make and use the invention commensurate in scope with the claims.

Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification, while being enabling for the treatment of Type II Diabetes, does not reasonably provide enablement for the prevention of any disease or the treatment of any disease other than Type II Diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention of claims 2 and 3 is the method of treating and preventing diseases characterized by misregulation of GSK-3, such as Alzheimer's Disease, stroke, atherosclerotic cardiovascular disease and cancer, etc.

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The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic and preventive effects of the above listed diseases, whether or not the disease is effected by the the mGluR5 receptor would make a difference.

Applicants' claims are therefore drawn to the treatment and prevention of Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and

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Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease.

(<[URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html](http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html)>.

Furthermore, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or event o treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease" (pg. 1994).

In regards to products for the treatment and prevention of stroke, stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, this trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Applicants claims encompass the treatment or prevention of various cancers. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531) Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment or prevention by the compound of the claims one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability, for example, since it is known that

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there is no known cure for Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

***The amount of direction or guidance present and the presence or absence of
working examples***

The only direction or guidance present in the instant specification is the listing of diseases applicant considers as treatable and preventable on pages 12 and 39 and assay data on page 37-38. There are no working examples present for the treatment or prevention of any specific disease or disorder. Additionally, the disclosure does not provide how this in vitro data correlates to the treatment or prevention of the assorted list of disorders of the instant claims.

Further, there is no disclosure regarding how all types of the diseases having diverse mechanisms are treated. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided of is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat or prevent the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is the method of treating a variety of disorders such as Alzheimer's disease, cancer, etc.

The disorders encompassed by the instant claims include, for example, disorders such as Alzheimer's disease, cancer, etc. some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all diseases would be benefited (treated or prevented) and would furthermore then have to determine which of the claimed compounds would provide treatment or prevention of which disease, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment and prevention of diseases claimed as a result necessitating one of skill to perform an exhaustive search for which diseases

can be treated or prevented by what compounds of the instant claims in order to practice the claimed invention. (Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not mean that the other diseases meet the enablement requirements).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that “ a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated or prevented by the compound encompassed in the instant claims, with no assurance of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571)

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272-0696. Mrs. Anderson can normally be reached Monday through Friday from 6:00am until 2:30pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*/Rebecca Anderson/
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30 March 2009